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(54) Method for the sequential oxidation of substituted quinolines to produce substituted-pyridine-2,3-dicarboxylic acids.

(57) The present invention provides a novel process for the preparation of substituted pyridine-2,3-dicarboxylic acids by the sequential peroxide-hypochlorite oxidations of substituted quinolines.

EP 0 388 619 A1

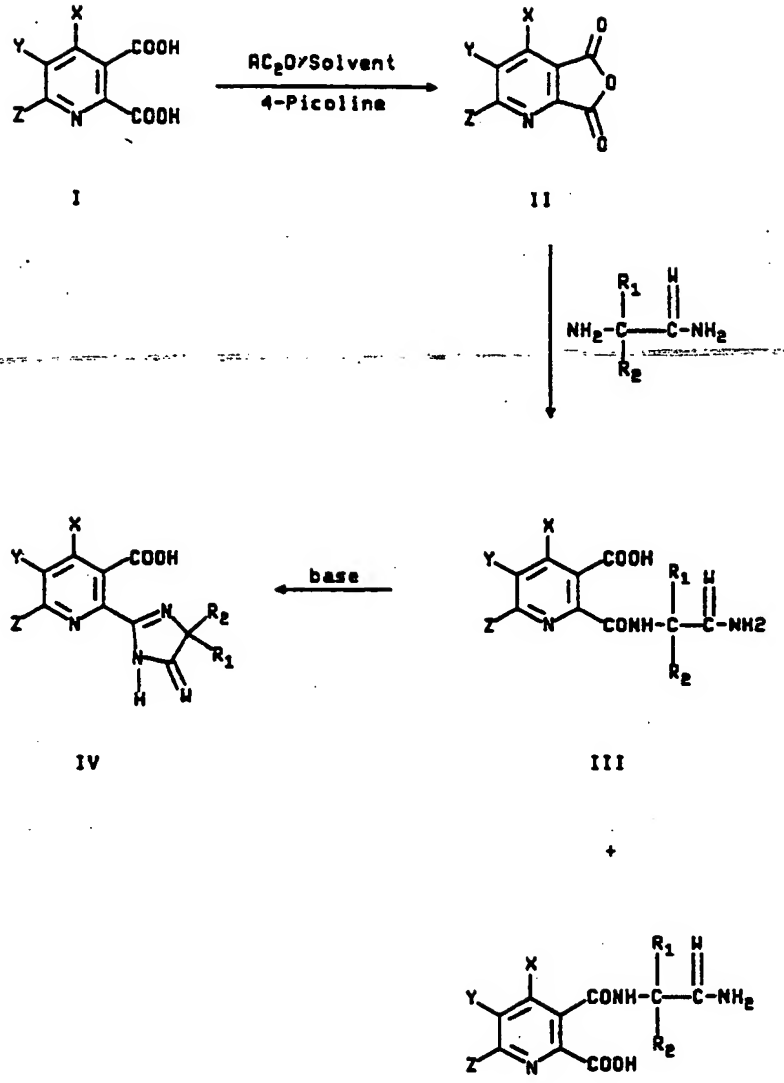
A METHOD FOR THE SEQUENTIAL OXIDATION OF SUBSTITUTED QUINOLINES TO PRODUCE SUBSTITUTED PYRIDINE-2,3-DICARBOXYLIC ACIDS

The invention herein described relates to a method for the preparation of substituted pyridine-2,3-dicarboxylic acids via a sequential two part oxidation of the appropriately substituted quinoline precursors under basic conditions. Related subject matter can be found in United States Letters Patent Number 4,816,588 which describes a method for the preparation of substituted and unsubstituted pyridine-2,3-dicarboxylic acids under basic conditions and the advantages thereof over the prior art. The novel use of hydrogen peroxide in the presence of base to yield substituted-2,3-pyridine-dicarboxylic acids in high purity is a distinct advantage over the known methods for preparing said dicarboxylic acids.

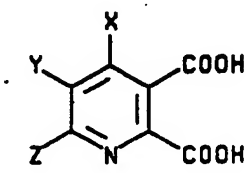
It is an object of this invention to provide an improvement in the hydrogen peroxide-base oxidation process so as to produce high purity 2,3-pyridine-dicarboxylic acids in significantly increased yields via a sequential oxidation using hypochlorite (introduced as its alkalai metal salt or generated in situ) in the presence of aqueous base.

It has been found that the sequential addition of hypochlorite to the hydrogen peroxide-base oxidation surprisingly decreases the amounts of hydrogen peroxide needed for optimum product purity and significantly increases the product yield. The substituted pyridine-2,3-dicarboxylic acids, so produced, are useful as intermediates in the preparation of novel pyridine and quinoline imidazolinone herbicidal agents as described in United States Patent 4,518,780 and United States Patent 4,638,068. The appropriately substituted pyridine and quinoline 2,3-dicarboxylic anhydrides used as starting materials in said patents may be prepared according to the process described in United States Patent 4,562,257 from their pyridine and quinoline 2,3-dicarboxylic acid precursors. The sequence of reactions described in the above mentioned United States Patents to obtain useful herbicidal agents of formula IV from substituted pyridine 2,3-dicarboxylic acids of formula I is illustrated as Flow Diagram I.

FLOW DIAGRAM I



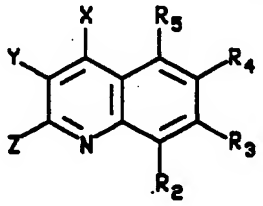
The invention relates to a novel method for the preparation of substituted pyridine-2,3-dicarboxylic acids of formula I



(I).

wherein
X is hydrogen, or methyl, with the proviso that when Y and Z are taken together to form a ring and YZ is represented by the structure: $-(CH_2)_n-$, where n is 3 or 4, X is hydrogen;
Y is hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, C_1-C_6 aminoalkyl, C_1-C_6 sulfonylalkyl, nitro, hydroxy, formyl, carboxy, acyl, amido, amino, C_1-C_4 alkylamino, diloweralkylamino, C_1-C_4 alkylsulfonyl, sulfonamido, or phenyl optionally substituted with one C_1-C_4 alkyl group, C_1-C_4 alkylsulfonyl group, halogen, hydroxy, or trifluoromethyl group;
Z is hydrogen, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, C_1-C_6 aminoalkyl, C_1-C_6 sulfonylalkyl, nitro, hydroxy, formyl, carboxy, acyl, amido, amino, C_1-C_4 alkylamino, diloweralkylamino, C_1-C_4 alkylsulfonyl, sulfonamido, or phenyl optionally substituted with one C_1-C_4 alkyl group, C_1-C_4 alkylsulfonyl group, halogen, hydroxy, or trifluoromethyl group; and when taken together,
Y and Z may form a ring in which YZ are represented by the structure: $-(CH_2)_n-$, where n is an integer selected from 3 or 4, provided that X is hydrogen; or

where L, M, Q, and R_1 each represent members selected from the group consisting of hydroxy, halogen, C_1-C_4 alkyl, C_1-C_4 alkylsulfonyl, C_1-C_4 haloalkylamino, C_1-C_4 alkylamino, diloweralkylamino, and trifluoromethyl, with the proviso that only one of L, M, Q or R_1 may represent a substituent other than hydrogen, halogen, or C_1-C_4 alkyl.
Compounds of formula I are prepared by oxidizing a substituted quinoline of formula II



(II)

wherein
X, Y, and Z are as described for formula I above,
R_2, R_3, R_4 and R_5 are each hydrogen, hydroxy, SO_3H, SO_2Cl, SH, halogen, NO_2, NH_2; with the proviso that one of R_2, R_3, R_4 or R_5 is other than hydrogen and when R_2 is hydroxy, at least one of R_3, R_4 and R_5 is other than hydrogen;
the N-oxides thereof; the acid addition salts thereof;
in the presence of aqueous base using hydrogen peroxide followed by addition of hypochlorite.

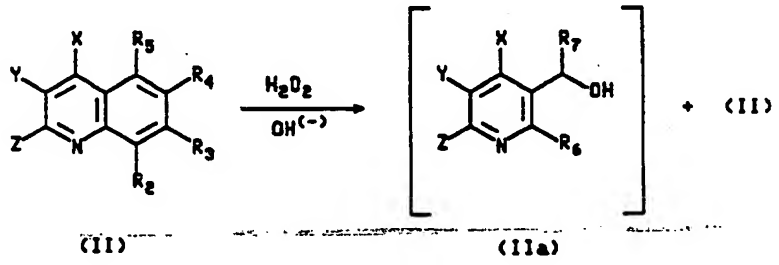
Aqueous bases suitable for use in the method of the invention include alkali metal and alkaline earth metal hydroxides and carbonates such as sodium, potassium, lithium, and calcium hydroxides or carbonates and mixtures thereof. Aqueous sodium hydroxide and aqueous potassium hydroxide are the preferred bases.

In the presence of 2.0-10.0 molar equivalents of aqueous base (preferably 5.0-6.0 molar equivalents), quinolines of formula II are treated with about 7.0-20.0 molar equivalents of hydrogen peroxide, preferably 7.5-9.0 molar equivalents, at 25°-125°C, preferably 85°-90°C. Following the addition, the reaction temperature is maintained for at least one hour at 25°-125°C, preferably 85°-90°C. The reaction mixture is cooled to a temperature between about 25°-90°C, preferably about 65°-70°C and mineral acid is added to obtain a pH of about 8-14, preferably about 10.5-11.5. At this time, 1.0-4.0 molar equivalents (preferably 1.0-2.0 molar equivalents) of hypochlorite anion is added as a 5%-30% aqueous solution or is generated in situ by the direct addition of chlorine gas. Reaction temperatures of above 25°-125°C are suitable, however, additional reaction time is required at lower temperatures for complete oxidation to occur.

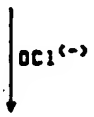
The oxidation of quinolines of formula II to pyridine-2,3-dicarboxylic acids of formula I according to the method of this invention is treated as a two part process. The initial step of the oxidation reaction is the

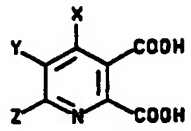
cleavage of the nonhetero-aromatic ring bearing the functional group by hydrogen peroxide in the presence of aqueous base to give intermediates of formula IIa. The second part of the process is the oxidation of the side chains of formula IIa intermediates to carboxylic acid functional groups via the introduction of hypochlorite anions as illustrated in flow diagram II.

FLOW DIAGRAM II



(II) (IIa)





(I)

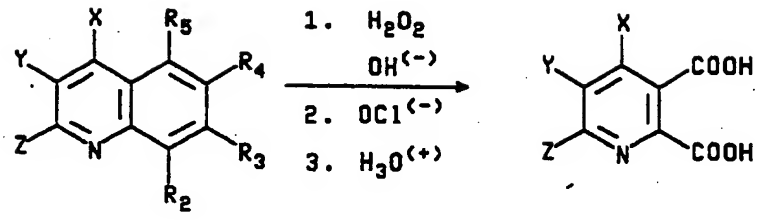
wherein R_6 and R_7 represent a mixture of members selected from the functional groups consisting of carboxylic acids, glycolic acids, aldehydes, hydroxymethyl groups, and other alkyl groups at intermediate stages of oxidation. It has been found that whereas hydrogen peroxide is preferable for the first oxidation step, i.e. cleavage of the aromatic ring system, surprisingly, hypochlorite anion is preferable for the completion of oxidation of the resulting intermediates to the final dicarboxylic acid products.

The pH of the reaction solution at the time of the introduction of the hypochlorite anion has a great influence on the reaction yield. It has been found that adjustment of the reaction pH to a range of about 10.5-11.5 gives an excellent yield of reaction product.

After the addition of hypochlorite as a 5%-30% aqueous solution or generated in situ by the addition of chlorine gas, the reaction is followed by using a potassium iodide-starch indicator test for the presence of hypochlorite anions. When the potassium iodide-starch test is negative (usually after about one hour), the product dicarboxylic acid can be obtained by acidification of the reaction mixture with a mineral acid and isolated by standard procedures such as filtration or extraction into an appropriate organic solvent such as tetrahydrofuran, acetone, a C_3-C_6 alcohol, or a mono C_1-C_4 ether of ethylene glycol. A preferred organic solvent is tetrahydrofuran.

Among the compounds that can be prepared by this process are those shown below in Table I.

Table I



(II) (I)

X	Y	Z
H	CH_3	H
H	C_2H_5	H
H	H	CH_3
CH_3	H	H
H	C_2H_5	C_2H_5
H	$H_2N-C_6-H_{12}$	H
H	Br	H
H	NH_2	H
H	NH_2	CH_3
H	$HOCH_2$	H
H	$CH_2=CH-CH_2$	CH_3
H	$CH_2=CH-CH_2$	H
H	$-SO_2NH_2$	CH_3
H	$CH_3-CH(OH)$	H

Formula II quinolines which may be used in the herein-described process are: 3-ethyl-8-chloroquinoline, 8-chloroquinoline, 3-methyl-8-chloroquinoline, 5-hydroxyquinoline, 8-quinolinesulfonylchloride, 8-(3-ethyl-quinoline)sulfonic acid, 8-quinoline sulfonic acid, 5-nitro-8-hydroxyquinoline, and the like.

In order to facilitate a further understanding of the invention, the following examples are presented primarily for the purpose of illustrating more specific details thereof. Unless otherwise noted, all parts are by weight and all degrees are degree centigrade.

EXAMPLE 1

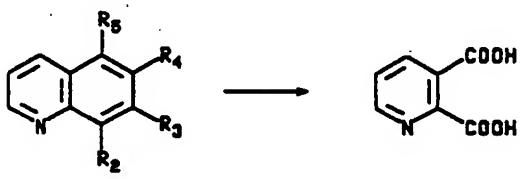
Preparation of pyridine-2,3-dicarboxylic acid via hydrogen peroxide and sodium hypochlorite

A stirred mixture of 8-aminoquinoline (7.21 g, 0.05 mole) and 15% aqueous potassium hydroxide (121.6 g, 0.325 mole) is treated with 8 molar equivalents of hydrogen peroxide as a 30% solution (45.3 g, 0.40 mole) at 80-90° over a one hour period. The reaction mixture is held at 80-90° for another 1/2 hour period, cooled to 65°, treated with 98% sulfuric acid to pH 11, and then treated with 15% sodium hypochlorite (44.7 g, 0.09 mole). The reaction temperature is maintained at a temperature between 65° and 70° for a total of 1 1/2 hours. The reaction mixture is cooled to 25° and the titled product is obtained in a 53.4% yield as determined by high pressure liquid-chromatography analysis.

Using the above procedure, pyridine-2,3-dicarboxylic acid is prepared using quinolines of formula III as shown in Table I.

Table I

Sequential oxidation of substituted quinolines to pyridine-2,3-dicarboxylic acid (PDC) via hydrogen peroxide and hypochlorite



(III)

Formula III Compound					Molar Equiv	% Yield
R_2	R_3	R_4	R_5	Base	Base	PDC
OH	H	H	Cl	KOH	5.5	53.6
NO_2	H	H	H	KOH	6.5	37.3
H	H	H	OH	KOH	5.5	58.5

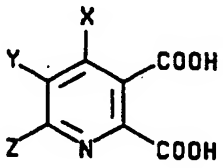
EXAMPLE 2

Preparation of pyridine-2,3-dicarboxylic acid via the sequential oxidation of 8-quinolinesulfonyl chloride

A stirred mixture of 25 mL of water and 8-quinolinesulfonyl chloride (11.4 g, 0.05 mole) is treated with 85% potassium hydroxide (24.2 g, 0.375 mole) and heated to 250° while distilling off some water. The reaction mixture is held at 250° for 1/2 hour, cooled to 20°-50° and treated with 100 mL of water. The reaction mixture is then heated to 85° and treated with 8 molar equivalents of 30% hydrogen peroxide (45.3 g, 0.4 mole) over a one hour period at 85°-90°. After an additional 1/2 hour at 85° and cooling to 65°, 98% sulfuric acid is added to pH 11, followed by the addition of 1.8 molar equivalents of 15% sodium hypochlorite (44.7 g, 0.09 mole) over a 1/2 hour period at 65°-70°. The reaction mixture is held for an additional 1 hour at 65°-70°, cooled to room temperature to give the product pyridine-2,3-dicarboxylic acid, as determined by high pressure liquid chromatography (HPLC) analysis.

Claims

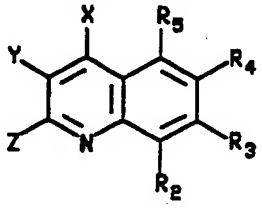
1. A method for the preparation of pyridine-2,3-dicarboxylic acids of formula I



(I)

wherein
X is hydrogen, or methyl, with the proviso that when Y and Z are taken together to form a ring, and YZ is represented by the structure: $-(CH_2)_n-$, where n is 3 or 4, X is hydrogen;
Y is hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, C_1-C_6 aminoalkyl, C_1-C_6 sulfonylalkyl, nitro, hydroxy, formyl, carboxy, acyl, amido, amino, C_1-C_4 alkylamino, diloweralkylamino, C_1-C_4 alkylsulfonyl, sulfonamido, or phenyl optionally substituted with one C_1-C_4 alkyl group, C_1-C_4 alkylsulfonyl group, halogen, hydroxy, or trifluoromethyl group;
Z is hydrogen, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, C_1-C_6 aminoalkyl, C_1-C_6 sulfonylalkyl, nitro, hydroxy, formyl, carboxy, acyl, amido, amino, C_1-C_4 alkylamino, diloweralkylamino, C_1-C_4 alkylsulfonyl, sulfonamido, or phenyl optionally substituted with one C_1-C_4 alkyl group, C_1-C_4 alkylsulfonyl group, halogen, hydroxy, or trifluoromethyl group; and when taken together,
Y and Z may form a ring in which YZ are represented by the structure: $-(CH_2)_n-$, where n is an integer selected from 3 or 4, provided that X is hydrogen; or

where L, M, Q, and R_1 each represent members selected from the group consisting of hydroxy, halogen, C_1-C_4 alkyl, C_1-C_4 alkylsulfonyl, C_1-C_6 haloalkylamino, C_1-C_6 alkylamino, diloweralkylamino, and trifluoromethyl, with the proviso that only one of L, M, Q or R_1 may represent a substituent other than hydrogen, halogen, or C_1-C_4 alkyl,
comprising reacting a quinoline compound of formula II



(II)

wherein
X, Y, and Z are as described for formula I above,
R_2, R_3, R_4 and R_5 are each hydrogen, hydroxy, SO_3H, SO_2Cl, SH, halogen, NO_2, NH_2; with the proviso that one of R_2, R_3, R_4 or R_5 is other than hydrogen and when R_2 is hydroxy at least one of R_3, R_4 and R_5 is other than hydrogen;
the N-oxides thereof; the acid addition salts thereof;
with about 7.0-20.0 molar equivalents of hydrogen peroxide in the presence of 2.0-10.0 molar equivalents of

aqueous base at a temperature range of about 25°C-125°C, cooling the thus-formed reaction mixture to a temperature below 125°C, treating the cooled reaction mixture with mineral acid to obtain a pH of about 8-14, treating the pH adjusted reaction mixture with 1.0-4.0 molar equivalents of hypochlorite and maintaining said reaction mixture at a temperature between about 25°C-125°C to yield the formula I pyridine-2,3-dicarboxylic acid.

2. A method according to claim 1 which further comprises isolating the formula I pyridine-2,3-dicarboxylic acid by acidification of said reaction mixture and extraction with an organic solvent.

3. A method according to claim 1 wherein about 7.5-9.0 molar equivalents of hydrogen peroxide and 5.0-6.0 molar equivalents of aqueous base are added to a stirred solution of a formula II quinoline.

4. A method according to claim 3 wherein the pH range of the reaction mixture is 10.5 to 11.5 at the time of the hypochlorite addition.

5. A method according to claim 4 wherein 1.0-2.0 molar equivalents of hypochlorite is generated in situ by the addition of chlorine gas.

6. A method according to claim 4 wherein 1.0-2.0 molar equivalents of hypochlorite is added as a 5%-15% aqueous solution.

7. A method according to claim 2 wherein the organic solvent is selected from a group consisting of tetrahydrofuran, acetone, C_3-C_5 alcohol, and mono C_1-C_4 ethers of ethylene glycol.

8. A method according to claim 7 wherein the organic solvent is tetrahydrofuran.

European Patent Office

EUROPEAN SEARCH REPORT

Application number

EP 90102551.0

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int Cl*)
A	EP - A1 - 0 149 857 (RÜTGERS WERKE) * Claim 1 * --	1	C 07 D 213/807
A	EP - A1 - 0 135 328 (APPLETON PAPERS) * Claim 1 * --	1	
A	EP - A1 - 0 126 893 (AM. CYANAMID) * Claims 1,3 *	1	

TECHNICAL FIELDS SEARCHED (Int Cl*)

C 07 D 213/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	30-04-1990	HOCHHAUSER

CATEGORY OF CITED DOCUMENTS

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